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pH sensitive core-shell magnetic nanoparticles for targeted drug delivery in cancer therapy

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Abstract

In the last decade, nanobiotechnology has evolved rapidly with an extensive impact on biomedical area. In order to improve bioavailability and minimize adverse effects, drug delivery systems based on magnetic nanocomposites are under development mainly for cancer imaging and antitumor therapy. In this regard, pH sensitive core-shell magnetic nanoparticles (NPs) with accurate controlled size and shape are synthesized by various modern methods, such as homogeneous precipitation, coprecipitation, microemulsion or polyol approaches, high temperature and hydrothermal reactions, sol–gel reactions, aerosol/vapor processes and sonolysis. Due to their unique combined physico-chemical and biological properties (such as higher dispensability, chemical and thermal stability, biocompatibility), pH responsive core-shell magnetic NPs are widely investigated for controlled release of cytostatic drugs into the tumor site by means of pH change: magnetite@silicon dioxide (Fe_3O_4@SiO_2), Fe_3O_4@titanium dioxide (TiO_2), *β*-thiopropionate–polyethylene glycol (PEG)-modified Fe_3O_4@mSiO_2, Fe_3O_4 NPs core coated with SiO_2 with an imidazole group modified PEG-polypeptide (mPEG-poly-L-Asparagine), polyacrylic acid (PAA) and folic acid (FA) coating of the iron oxide NP core, methoxy polyethylene glycol–*block*–polymethacrylic acid–*block*–polyglycerol monomethacrylate (MPEG–*b*–PMAA–*b*–PGMA) attached by a PGMA block to a Fe_3O_4 core, PEG-modified polyamidoamine (PAMAM) dendrimer shell with Fe_3O_4 core and mesoporous silica coated on Fe_3O_4, mostly coated with an anticancer drug. This review paper highlights the modern research directions currently employed to demonstrate the utility of the pH responsive core-shell magnetic NPs in diagnosis and treatment of oncological diseases.

Keywords: core-shell magnetic nanoparticles, pH sensitive, targeted drug delivery, cancer therapy.

Introduction

Cancer is one of the main causes of high rates of mortality and morbidity worldwide; recently, it has outpaced heart diseases as the leading cause of death. In the last century, chemotherapy ceased to be a viable therapeutic approach for the treatment of cancer because it lacks specificity, affecting in the same extent the healthy cells. Chemotherapy uses powerful anticancer drugs that are unspecific and cause severe side effects, due to their cell toxicity. The main challenge in chemotherapy is the delivery of an adequate dosage of a given cytotoxic agent directly to the tumor, while diminishing the adverse side effects by limiting their action against healthy tissue. Another disadvantage of chemotherapy is the lack of tumor-specific targeting, which can also result in weak immune system and liver damage. In order to overcome the disadvantages of traditional chemotherapy, drug delivery systems are used to improve the pharmacological properties of the drug [1–10].

Nanotechnology is evolving very fast and is expected to have a considerable impact in the medical field, mainly in cancer research. Drug delivery systems, based on nanoparticles (containing encapsulated pharmaceutical agents, especially anticancer drugs), are under development in order to improve drug bioavailability and avoid side effects. Moreover, conceiving these nanoparticles as multifunctional stimuli sensitive carriers will improve the effectiveness of many cytostatic drugs. Among the expected characteristics of targeted drug delivery systems, we can include: longer persistence in the organism fluids (*e.g.*, blood) and the ability to react to local stimuli, for example to release an encapsulated therapeutic agent under pH change. pH sensitive drug delivery systems have gained significant importance due to their unique properties; their major advantage is that they can deliver the drug at a specific moment. pH sensitive drug delivery systems are promising in many disease treatments, as ulcer, asthma, cardiovascular diseases, cancer and hyper-tension. Many nanodimensional carriers adopt the approach of pH difference in order to target the drug at the tumor site. Moreover, anticancer drugs can be either attached or encapsulated in pH responsive polymers [11–21].

The architecture and development of effective new drug delivery systems has been well investigated in the last years. In the traditional drug delivery approach, the concentration of the drug in blood increases rapidly and

drops after a short time, depending on some physico-chemical aspects of the drug. The main goal is to develop an optimal drug delivery system, which will maintain the drug concentration in the chosen therapeutic range. Stimuli sensitive nanomaterials have shown a considerable higher potential than classical drug delivery systems. Apart from the other stimuli, pH responsive systems have been extensively used to obtain and improve nanoscale drug delivery systems efficient in the cancer treatment [12, 22–27].

The main advantages of using nanoparticles drug delivery systems refer to the fact that they have the capacity to target specific body sites, reduce the drug level in plasma and minimize unwanted side effects on non-targeted sites [28]. As a rule, the pH of a pathological tissue is lower than the pH of a normal tissue, for example at the site of inflammation the pH can decrease from 7.4 to 6.5. The tumor microenvironment is highly acidic compared to normal tissue, due to the active metabolism of the tumors cells, this means that they divide chaotically and at a significantly higher rate than normal, healthy cells. pH sensitive drug delivery systems have been realized, with drug release specifically activated by the acidity of the tumor microenvironment [22, 29].

⊟ Magnetic nanoparticles as drug carriers

Paul Ehrlich (1854–1915) stated that if an agent could selectively spot an organism that causes a disease, without harming normal cells, it will be considered as a "magic bullet". Since then, many approaches were proposed in order to delivery drugs to the tumor sites. Magnetic nanoparticles were proposed in 1960 as drug carriers for the delivery of pharmaceutical agents through the vascular system to a specific body part, with the help of a magnetic field [28].

In targeted sites of a pig liver, it was observed the extravasation of the magnetic nanosized carriers once the magnetic field is removed. In studies using an external magnet (Nb–Fe–B) and the same magnetic nanocarriers (with an incorporated anticancer drug – doxorubicin), it was concluded that small nanosized carriers can enter easily, even in difficult to reach tumors, thus making them of important use in tumor targeted drug delivery systems. The first clinical trial using magnetically targeted nanoparticles as drug carriers was realized in 1997. These nanoparticles were used to deliver an anticancer drug (4'-epidoxorubicin) to 14 patients that had advanced solid tumors. These nanosized complexes were made of clusters of magnetite, coated with a hydroglucose polymer, with the drug reversibly absorbed on the surface. A strong magnet (Nb–Fe–B) was placed on the skin in the area of the tumor, providing an external magnetic field. The study had positive results for seven of the 14 patients that were included in the clinical trial [30].

FeRX Inc., founded in 1997, developed doxorubicin loaded magnetic nanoparticles made of metallic Fe and activated carbon. In a clinical study, patients with primary liver cancer were treated with this type of nanoparticles (NPs). However, the study did not conclude with favorable results. Successful results in animal models were showed by mitoxantrone loaded TargetMAG-doxorubicin NPs, that consisted in a magnetite core and a cross-linked matrix

with terminal cations that can be changed reversibly by the positive charged doxorubicin [28].

The polymeric nanoparticles liposomes have been examined as nanosized vectors for drug delivery. However, these nanoparticles presented many disadvantages such as high cost, non-specific drug release and low chemical and mechanical stability. Among these issues of polymeric nanoparticles, high polydispersity is the most important. The alternative would have been using dendrimers, that have monodisperse character, but they involve high costs. Because of the disadvantages of the organic NPs, mixed inorganic–organic magnetic nanoparticles have been investigated [28].

Magnetic nanoparticles have been extensively used in medical applications due to their specific properties. They have a length of 1 nm up to 100 nm in at least one dimension. Magnetic NPs are composed of magnetic elements such as iron, nickel, cobalt and their oxides. They become popular as drug carriers due to their unique properties, biocompatibility and capability to be controlled by an external magnetic field. Their main advantage is the drug transport to a specific area of the body, releasing it in a controlled manner (administrating a correct dosage of drug) without damaging other tissues. Magnetic NPs as drug carriers in drug delivery systems are used because these nanoparticles become magnetic if an external magnetic field is applied. The therapeutic agent can be either attached to the magnetic NPs surface or encapsulated in a mixture of polymer and magnetic NPs. After the compound is injected to the patient and reaches the targeted site, the drug in released due to changes in pH, temperature, enzymatic activity or osmolality [1, 2, 19, 31–33].

The behavior of a magnetic nanoparticle can be influenced by its surface chemistry, such as size and magnetic properties. This is a very important factor when talking about the immune system mechanisms; the specific properties of these carrier type NPs can assure that the reticuloendothelial system (RES), which can ingest and destroy unwanted foreign materials, can be avoided. In order to increase the circulatory half-life, magnetic NPs can be coated with neutral and hydrophilic compounds, such as polyethylene glycol (PEG) and polysaccharides, or have reduced sizes. Passive transport of magnetic NPs to the specific site through blood flow is the fundamental part of *in vivo* applications. When designing magnetic nanoparticles-based systems, it is very important to take into consideration the magnetic NPs circulation pharmaco-kinetics. The factors that govern the pharmacokinetics of magnetic nanoparticles are surface characteristics and the hydrodynamic size. RES is the basic physiological mechanism accountable for nanoparticles clearance from circulation. The above-mentioned factors, in interaction with RES, determine plasma lifetime [28, 34].

Magnetic NPs have biological functions that are governed by their manageable physiochemical properties such as size, shape, hydrophobicity and surface charge. In order to have control over the magnetic NPs abilities to target, carry and deliver the drug, particle size and size distribution is crucial. Due to the hydrophobicity of the magnetic nanoparticles surface, the proteins from the blood circulation are absorbed. The action in which these proteins bond to the surface of the nanoparticles is

called opsonization. If there is a lot of opsonization, the NPs can be easily removed by macrophages. However, if nanoparticles are needed for a long period of time in the organism, opsonization can be minimized by coating the nanoparticles surface with hydrophilic polymers or surfactants. The predetermined course of magnetic NPs depends on the dose and administration route that can be, for example, oral, intravenous or transdermal [28, 31].

To design efficient magnetic NPs as carriers for specific locations in drug delivery, they need to contain on their surface or encapsulate in their platform a pharmaceutical drug. This drug must be driven to the desired location and released there. Bioavailability of the NPs in the human body, as well as blood circulation time, is strongly related to the size, charge and surface chemistry of the magnetic nanoparticles. For example, large particles (200 nm) are isolated in the spleen by mechanical filtration and eliminated by phagocyte systems and that leads to a reduction of blood circulation time. Moreover, small particles (<10 nm) are easily eliminated through extravasation. The ones that show the best blood circulation times have a dimension between 10 nm and 100 nm, because they can easily evade the RES and also can pass through small capillaries [1, 2, 35].

Another important factor that made magnetic NPs desired in targeted drug delivery systems for tumors is the size influence on magnetic properties and surface features. Small ferromagnetic or ferrimagnetic NPs, with diameter <10 nm, tend to become superparamagnetic [1, 2, 36]. The main advantage of such particles is the obtention of stable suspensions in the absence of a magnetic field; in the same situation, as comparison, larger magnetic particles tend to form aggregates (clusters). The behavior in the presence of a magnetic field is similar for small or large particles; in both cases, a strong magnet can guide them in to the body. Magnetic nanoparticles without coating have hydrophobic surfaces and a large surface area to volume ratio. Because of the hydrophobic interactions between particles, non-coated magnetic NPs become larger in size, forming clusters. These clusters perform strong magnetic dipole–dipole attraction to each other and display ferromagnetic behavior. One magnetic cluster can magnetize another clusters (mutual magnetization), resulting in a rise of the aggregation properties. Moreover, because the magnetic particles are attracted magnetically, they exhibit flocculation as a result of van der Waals forces. The surface coating is also an important feature that helps to avoid agglomeration and opsonization. It has been shown that if the magnetic NPs are coated with biocompatible materials, they present lower toxicity [31].

In order to achieve magnetic NPs stabilization, a high coating density is preferable. Stabilizers such as surfactants or polymers are supplemented at the time of preparation, so that the agglomeration of nanoparticles is avoided. Synthetic polymers, such as poly (lactic-*co*-glycolic acid) (PLGA), polyethylene glycol (PEG), polyvinylpyrrolidone (PVP) can be used. As natural polymers, gelatin, chitosan or dextran may be also be used. To enable the dispensability in aqueous media, surfactants such as dodecylamine are very important [35].

Magnetite is the most used magnetic compound for

nanoparticles, therefore is being used in various biomedical applications [37].

The main challenge in the last years is to elaborate a method that can concentrate a high amount of anticancer drug in the cancer tissue and in the same time only a limited amount of drug harming the healthy tissue. For this, studies were made using magnetic nanoparticles as drug carriers. A recent study reported NPs that were injected into the blood flow and kept in the tumor site by means of a strong magnetic field. In order to do this, an iron oxide core was covered by a layer of polymers that made them tolerable in the body. Moreover, an anticancer drug, mitoxantrone, was bound to the phosphate groups of starch derivatives. This system was used onto female rabbits; no side effects were registered. Remarkably, in 35 days after the treatment, the tumor completely disappeared [6].

Many advantages can be obtained by coating magnetic NPs; the coating promotes the stabilization of the NPs in environments with alkaline pH or considerable high salt concentration [1, 2, 19, 32, 38]. Silica coatings provide supplementary advantages. For example, the external surface of this coating can be functionalized and thus promoting biomolecules binding. This is a result of the presence of hydroxyl surface groups, which will allow surface attachment by covalent connection of specific biomolecules. Drugs can also be attached due to another factor: the internal porosity of silica. While passing through the blood flow, different antibodies can bind to the surface and accelerate the phagocytosis of these nanoparticles. In order to avoid this, biodegradable and nanosized biodegradable inorganic and organic coatings are used by way of detecting and uptake by the macrophages of the RES. For this aim, the most used coating is polyethylene glycol (PEG), which comes with the advantages of delaying the action of the RES, low toxicity and immunogenicity. The nature of the coating is very important when surface functionalization may cause agglomeration of NPs. In these cases, the modification of the surface can diminish the aggregation and boost the nanoparticle stability in body fluids [28].

Other factors, such as magnetic properties and the size of the particles, the strength of the magnetic field, the drug stocking capacity and the blood flow rate should be taken into consideration when crafting magnetic drug delivery systems [39].

The only type of magnetic nanoparticles, approved by the *Food and Drug Administration* (FDA) for clinical use are iron oxide NPs. Along with biocompatibility and biological activity, some other factors, such as one-step synthesis by alkaline co-precipitation of Fe^{2+} and Fe^{3+}, chemical stability and chemical modification by coating iron oxide cores with different shells, contributed to these approval. Moreover, iron oxides (magnetite and maghemite) can be found naturally in the human heart, spleen and liver, which prove that they are biocompatible and non-toxic [39].

Another biomedical application of the iron oxide-based NPs that have superparamagnetic behavior and functionalized surface is the extensively studied hyperthermic treatment of tumors. Hyperthermia is strongly linked to cancer therapy; this is a method in which body tissue is subjected to high temperatures, in the interest

of damaging and killing cancerous cells or making them more susceptible to the effects of radiation or specific anticancer drugs. Along with hyperthermia, many other methods that use laser or radiation have specific properties, which may be related with side effects in healthy tissues. Concerning this issue, researches have been made to find other methods that use high temperature on tumor areas, without affecting the healthy tissues. Magnetic hyperthermia favors local heat through magnetic NPs under the influence of a magnetic field. The ability of magnetic NPs to convert electromagnetic energy into heat permits a high temperature in specific areas, where the cancerous cells and the nanoparticles are placed; these NPs can be managed externally by a magnetic field. The electromagnetic radiation used by magnetic hyperthermia is completely harmless and can easily pass through the tissues, in order to reach the central core of the magnetic material. This method has a high specificity, because of the sensitivity of cancerous cells to temperatures higher than $42^{0}C$. At this temperature, the enzymes that keep the cells alive are destroyed and therefore the selective extermination begins. The magnetic NPs used in this method should have a superparamagnetic behavior and furthermore, if the particles are bigger, high saturation and better efficiency are achieved for magnetic hyperthermia applications. However, it is not desired that the particles should cross a limit of size and become ferromagnetic because of the aggregation phenomena; a compromise must be realized between the size of the particles and their magnetic properties. Very small particles cannot produce a hyperthermic effect, whereas extremely large particles cannot cross the endothelial barrier [40].

Superparamagnetic iron oxide nanoparticles (SPIONs) are made of an iron oxide core that can be delivered to a specific site through an external magnetic field. They show unique properties such as superparamagnetism, high field irreversibility, high saturation field, extra-anisotropy contribution or shifted loops after field cooling. Because of these properties, SPIONs do not present magnetic interaction after the removal of the external magnetic field. Since 1970, when the idea of combining magnetic carriers with an external magnetic field was established, a vast amount of magnetic NPs has been defined as drug delivery carriers to specific target locations [1, 2, 26, 36]. SPIONs have two configurations: one is a core-shell structure, in which the core is made of magnetic nanoparticles (magnetite and maghemite) and the shell is a biocompatible polymer; the other one is obtained by the precipitation of SPIONs inside the pores of a porous biocompatible polymer. The coating is considered as a protection to the magnetic core against the surrounding environment. SPIONs can also be functionalized by attaching carboxyl groups or molecules in the concern of increasing targeting properties. The functionalization of this NPs acts as an attachment surface for the connection of therapeutic drugs to the carrier complex. In order to use SPIONs as magnetically targeted carriers, controlled by an external magnetic field, several parameters must be taken into consideration: the field and the gradient strength, the volumetric and magnetic properties of the magnetic nanoparticles [1, 2, 26, 36]. To successfully deliver the SPIONs to the desired site, the forces exerted by the external magnetic field must overcome the forces exerted by the blood flow. The particles are usually managed by an external magnet (*e.g.*, Nd–Fe–B), placed outside the body, in the proximity of the desired location. The drug carrier complex is usually injected into the patient via the blood flow. Once the forces exerted by the magnetic field overcome the linear blood flow rates and the complex reaches the targeted site, the drug in release either by enzymatic activity or by changes in physiological conditions (*e.g.*, pH) [1, 2, 26, 36, 41].

Another extensive uses of magnetite biocompatible SPIONs in biomedical applications is the magnetic resonance imaging (MRI), targeted release of anticancer agents, hyperthermia and magnetic field assisted radionuclide therapy. In the concern of using SPIONs in medical therapy, they have to be stable in water, at physiological pH and salinity; this stability is strictly related to the particle size. Another important factor is related to surface functionalization. SPIONs surface properties can be controlled by coating with a biocompatible polymer, either in the synthesis process of or after; the coating layer prevents the formation of large clusters. Biocompatibility and toxicity of SPIONs must be taken also into consideration when intended to be used into the human body. The nature of the magnetically sensitive item and the final dimension of the particle, including the core and the shell, are important factors that determine the biocompatibility and the toxicity of the magnetic NPs [2, 26, 41].

The fabrication methods used for nanoparticles can usually be found in the category of "bottom-up" methods, in which nanobiomaterials are prepared in a controlled fashion, from atoms and molecules. These methods are thermodynamically monitored by the self-assembly process. Some biomedical applications require the use of core-shell magnetic NPs [8, 10, 42–44]. The nanoparticles have a metallic or metallic oxide core, encased in an inorganic or a polymeric coating that increases the nanoparticles biocompatibility, and might serve as a support for biomolecules. Attaching drugs to magnetic NPs can be realized in many ways, such as covalent binding, electrostatic interactions, adsorption or encapsulation processes. The transport of magnetic NPs that contain drugs to the desired site can be realized by passive or active mechanisms [8, 10, 42–44]. Active mechanisms depend on the attractiveness of the nanoparticles to the damaged location by using recognition ligands, for example antibodies, that are connected to the surface of the magnetic NPs and by the manipulation of an external magnetic field. On the other hand, passive mechanisms are based on the enhanced vascular permeability and retention (EPR) of the tumor tissues [39].

⊞ Synthesis methods of magnetic nanoparticles

Methods based on preparation from solution allow the formation of magnetic NPs with precise controlled size and shape in a simple manner.

Homogeneous precipitation

Homogeneous precipitation methods are used in order to achieve uniform particles. These methods have as basis the separation of the nucleation and growth of the nuclei.

When the concentration of continuant species attains critical supersaturation, one short burst of nucleation appears and so the nuclei are synthesized. They can grow consistently by means of diffusion of the solutes from the solution on their surface, up to when they achieve their final size. These two phases must be distinct in order to attain monodispersity, meaning that once the growth process is established, nucleation must be avoided. However, uniform shaped nanoparticles have also been realized after numerous nucleation events, the final uniform shape being attained by self-sharpening growth process [45].

Coprecipitation

The coprecipitation method is probably the easiest and most efficient synthesis method used to achieve magnetic NPs. Iron oxides, magnetite or maghemite, are usually processed using stoichiometric mixtures of ferrous and ferric salts, in an aqueous environment. Magnetite can be converted into maghemite by means of air oxidation. In order to obtain magnetite spherical particles in solution, there are two principal synthesis procedures. The first one is based on ferrous hydroxide suspensions that are partially oxidized with various oxidizing agents. In the second method, stoichiometric mixtures of ferrous and ferric hydroxides are obtained in aqueous solutions, reaching homogeneous sized and spherical magnetite particles. It is likely to manage the particles size by tailoring the pH and the ionic strength of the precipitation medium. Using this method, the main asset is that a big amount of magnetic NPs can be synthesized. However, the downside is that the particle size distribution cannot be controlled [45, 46].

Microemulsion methods

Water-in-oil (*w/o*) microemulsions are liquid solutions with properties as thermodynamic stability, isotropy, transparence and are also simple and versatile starting materials which can furnish nanosized particles. This type of systems consists of a continuous oil phase, in which dispersed assemblies of surfactant molecules can be found. In these assemblies of surfactant molecules, there are entrapped microdroplets of the aqueous phase. The limitation of particle nucleation, growth and cluster formation is given by the surfactant-stabilized micro-cavities. There have been conducted studies using this synthesis method, the result being magnetic NPs with an average size of 4 nm up to 12 nm and a standard deviation of 0.2 up to 0.3. These types of emulsions are used to synthesize superparamagnetic iron oxide nanoparticles with controlled size and shape. The main asset of this method is the controlled size of the NPs that can be obtained by managing the dimension of the aqueous droplets core [45, 46].

Polyol method

Polyol solvents, such as PEG, have unique properties: from the dielectric point of view, they behave as solvents capable to dissolve inorganic compounds; from their high boiling point of view, they present a large operating temperature range in the concern of synthesis of inorganic compounds. The polyol liquid is the solvent of the metallic precursor and the reducing agent. The metallic precursor can be either very soluble or lightly soluble in the polyol. The solution is then mixed up and heated to a given temperature. Non-aggregated and well-defined particles can be obtained by managing the kinetics of reactions in solution. The polyol method was the first technique that used noble metals (*e.g.*, gold) and nickel, cobalt or copper. Recently, the method has widespread and was used to synthesize other materials, as iron based alloys. Non-aggregated magnetite nanoparticles can be synthesized using the polyol process [45, 46].

High temperature and hydrothermal reactions

Dispersible magnetic iron oxide NPs can be obtained by the decomposition of Fe precursors in the proximity of hot organic surfactants. Hydrothermal synthesis of Fe_3O_4 is realized in aqueous media, in reactors with sustain high pressures and temperatures. There are two reactions that can result in the formation of ferrites: hydrolysis and oxidation of mixed metal hydroxides. The only difference between the two is that in hydrolysis, ferrous salts are used. The main characteristics that have an impact on the final product are temperature, time and the solvent. If during the reaction time is longer, the size range of the Fe_3O_4 powders is higher. Using thermal decomposition, hydrophobic magnetite particles were synthesized from $Fe(CO)_5$ in an octylether solution of oleic acid [45, 46].

Sol–gel reactions

The sol–gel process uses molecular precursors that go through hydroxylation and condensation in a solution. The reactions are conducted at room temperature, thus additional heat treatments is needed in order to achieve the final crystalline shape. Solvent, temperature, concentration and pH are some of the parameters that influence in properties of the gel. This method can attain strict control over the particle size, monodispersity and predetermined structure. An example is the synthesis of maghemite NPs with a size range between 6 nm and 15 nm, after a heat treatment of the gels at high temperature (400^0C) [46].

Aerosol/vapor methods

Precise shaped and sized magnetic nanoparticles can be obtained using spray and laser pyrolysis. These methods have a high manufacturer rate that foresees a promising future for the synthesis of magnetic NPs used *in vivo* and *in vitro* applications.

In spray pyrolysis process, a solid is obtained by spraying a solution in a succession of reactors. In these reactors, the aerosol droplets are subjected to evaporation of the solvent and solute condensation in the droplet. The following step is drying and thermolysis of the precipitation particle at higher temperatures. Finally, the results are microporous solids, from which in the end dense particles are formed. The shape and size of the final particles can be managed from the original droplets.

Laser pyrolysis consists in heating a flowing mixture of gases with a continuous wave carbon dioxide laser. The laser initiates and maintains a chemical reaction. This method can manufacture small sized particles, with narrow particle size distribution and also an almost absence of aggregation. By using a one-step CO_2 laser pyrolysis

method, γ-Fe$_2$O$_3$ NPs can be attained with the use of Fe(CO)$_5$ as precursor [45].

Sonolysis

Iron oxide can be synthesized by sonolysis of organo-metallic precursors. High temperature is generated by the fast collapse of the cavities (cavitation process) and ferrous salts are conversed into magnetite NPs [46].

⊟ pH sensitive core-shell magnetic nanoparticles

In the last years, there had been an intense interest in the manufacturing of core-shell magnetic NPs. Core-shell magnetic nanoparticles can merge the magnetic properties given by magnetic NPs as the core and the properties of the shell, depending on the material [47].

Core-shell NPs have unique combined properties such as lower cytotoxicity, higher dispensability, biocompatibility and chemical and thermal stability. Occasionally, the shell does not only have the property of increasing biocompatibility, but also of improving the cores properties. The hydrophobicity of nanoparticles is an important aspect when the NPs are dispersed in aqueous media. Core-shell nanoparticles have been intensively investigated in the field of cancer therapy. The core is coated with a convenient shell in the concern of increasing biocompatibility and pharmacokinetic properties in the human body. The anticancer agent is either attached or encapsulated in/on the core-shell complex. Higher surface leads to higher drug storing capacity. Surface modification must be made in respect of releasing the anticancer agent in the tumor site by means of changes in the pH values [48].

The pH value of damaged tissues, when affected by inflammation, infection or cancer is substantially different than the pH of healthy tissues. For example, if the tissue is subjected to a 60-hour inflammatory reaction, its pH value drops from 7.4 to 6.5. This specific variation can be used for the development of pH sensitive drug delivery systems that can achieve the biochemical properties at the specific location for targeted drug delivery. Anticancer treatment is usually associated with severe side effects, due to non-specific release of drugs into the healthy tissue. Specific targeting of pharmaceutical drugs in the tumor site is highly important in cancer therapy [49].

In core-shell nanoparticles with directly connected functionalities, the shell must be made of organic or inorganic materials that are directly grown or connected to the magnetic core in order to achieve another performance apart from their magnetic one. Magnetic NPs have been widely used in biomedical applications that require high biocompatibility; therefore, surface functionalization is an essential requirement in the interest of making them applicable in this field. Multifunctionalized nanocomposites consist of a chemotherapeutic agent (discharged by a pH sensitive mechanism), a specific ligand that can relate to tumor cells and iron oxide NPs as a core [50].

In order to accomplish adequate tumor specific drug delivery it is very important that the drug carriers make a difference between healthy and tumor cells, morphologically or physiologically. Tumor cells have a very fast growth and metabolic rate, which leads to a low intracellular pH. One way to deliver drugs to cancerous cells is to attach specific nutrients for tumors to the drug carriers, so that cancerous cells will correlate with the drug vesicle much faster than normal body cells. Moreover, the drug-embedding nanovesicles can be designed in such manner that they can release their load in response to the lightly acidic pH. Only when the drug carrier arrives at the specific site, the pharmaceutical drug is released directly into the blood flow by means of changes in temperature or pH. Stimuli-sensitive polymers are a one of the kind category of polymers that react to the changes in environmental conditions, such as pH, temperature and electric field. When combining stimuli-responsive polymers with magnetic NPs and cancer targeting characteristics, the result is a compelling drug delivery system with controlled drug release [51].

Core-shell structures containing iron oxides are intensively used in order to achieve multifunctional magnetic nanoparticles systems. Even though iron oxides have many crystalline polymorphs, only magnetite (Fe$_3$O$_4$) and maghemite (γ-Fe$_2$O$_3$) are used in biomedical applications. Their surface chemistry and functionalization can also be easily fashioned. In order to improve drug delivery, adequate surface coating must be realized to become an integral component of a multifunctional magnetic NPs platform. To achieve this, an iron oxide core can be coated with organic materials (*e.g.*, PEG), inorganic materials (*e.g.*, gold) or oxides (*e.g.*, silica) [52].

The magnetic polymer-coated NPs, loaded with specific tumor drug is guided to the desired location by means of an external magnetic field. When the magnetic field is removed, the nanovesicles will detect the cancerous cells by tumor recognition function and the drug will be released because of the change in pH (from physiological pH – 7.4 to endosomal pH – 5.3). The drug release can be accelerated by a magnetic field [51].

pH responsive polymers can modify their size in function of the changes in the pH of the surrounding environment, resulting in a expansion or a collapse, depending on the pH of the media. This behavior is due to the existence of specific functional groups in the polymer chains. The pH sensitive materials can be classified in two groups. In the first one there are polymers containing acidic groups, such as –COOH, which expand in basic pH (*e.g.*, polyacrylic acid). The second one consists of polymers with basic groups, as –NH$_2$, which swell in acidic pH (case of chitosan). pH dependent expansion of nanogels can also be used for the drugs loading. When the pH-sensitive nanosized gel swells, the permeability increases, thus allowing the encapsulation of NPs or the release of an already incorporated drug [53].

Drug absorption is influenced by its solubility and availability of specific blow flow in tissues and this is a cause for which the concentration of drug in the blood depends on the amount of drug delivered by the drug delivery system. The main ways to deliver drugs in the body are oral, injection, implant, transdermic or mucosal. In conventional administration route, the drug is introduced in the body in periodic dosages; in the controlled release case, the polymer system delivers the drug in an optimal dosage for a prolonged period of time, by that intensifying its efficiency and boosting patient compliance [53].

⬚ Applications in cancer therapy

Cancer is known to be the leading cause of mortality worldwide. This cause is determined by the rapid and uncontrolled cell growth. The most used treatment to kill cancerous cells is chemotherapy. However, chemotherapy treatment comes with severe sides effects, because of its lack of specificity, affecting also healthy cells. In order to overcome the downsides of chemotherapy, an effective approach is the use of systemic nanomedicine with anticancer drugs. Presently, multifunctional nanoparticles platforms have been used as target drug delivery systems. Magnetic nanoparticles coated with polymeric materials have higher stability, superparamagnetism and suitable biocompatibility as drug vesicles [54].

There were studies that realize a β-thiopropionate-polyethylene glycol-modified Fe_3O_4@$mSiO_2$ nanocomposites as drug delivery systems with controlled released established on the endosomal pH of tumors. Doxorubicin (DOX) was used as an anticancer drug. After DOX was loaded, β-thiopropionate-polyethylene glycol (P2) was grafted onto Fe_3O_4@$mSiO_2$ as a blocking shell, in order to prevent a premature drug release. The shell makes possible the drug releasing only when the optimal pH is reached, otherwise the shell remaining closed [54].

In some studies, polyacrylic acid (PAA) was chosen as a pH-sensitive polymer coating for magnetic NPs. Because magnetic nanoparticles are not stable enough in acid media, PAA is grafted to it by means of electrostatic interactions in order to increase the stability. Specific ligands, such as folic acid (FA) combined with PAA, have proven high encapsulation efficiency and capacity and a good pH sensitive release profile. The anticancer drug attached was DOX. It was shown that PAA and FA shell could encapsulate a big amount of DOX and showed remarkable efficiency for targeting [55].

Nanomaterials are intense researched because of their unique properties that make them promising for biomedical applications. Magnetic nanoparticles have superparamagnetic properties, meaning that when the magnetic field is removed, they can redisperse. Core-shell magnetite hybrid NPs have the advantage of high stability against oxidation and also, because of the polymeric shell, a great amount of drug can be encapsulated. Poly-2-dimethylaminoethylmethacrylate (PDMAEMA) has excellent properties, such as biocompatibility, hydrophilicity and pH responsivity, which make them suitable for medical and pharmaceutical studies. If the pH value of the media is modified, magnetite NPs coated with PDMAEMA cannot only deliver the drug to the desired site, but also control the rate of drug releasing. Research on this behalf showed efficiently controlled drug release with PDMAEMA coated Fe_3O_4 NPs, this kind of magnetite hybrid nanoparticles can be anticipated to be used as targeted drug delivery systems with controlled release rate [56].

Block copolymers can be anchored to Fe_3O_4 NPs in order to increase their stability and dispersity. Still, even though polymer coated magnetic NPs had increased stability, the active nanoparticles cannot be stabilized, therefore are not stable in blood. In order to protect the magnetic nanoparticles, biocompatible silica can be precisely attached to the magnetic nanoparticles and form Fe_3O_4@SiO_2 core-shell structures. This structure shows stability in acidic pH and easy control of the shell consistency. The silica shell preserves the magnetism of Fe_3O_4. However, Fe_3O_4@SiO_2 cannot load drugs properly, so the need of a more complex system is desired. Multifunctional hybrid NPs were obtained by attaching to the silica coating the biocompatible block polymer polyethylene glycol-*block*-polyaspartic acid (PEG-*b*-PAsp). This enabled the stabilization of the magnetic NPs and also avoided absorption. PAsp was used in order to encapsulate the therapeutic drug (DOX) *via* electrostatic interaction. This kind of hybrid NPs showed great potential applications in cancer therapy as targeting drug delivery carriers [57].

Nanoparticles smaller than 200 nm will avoid the RES recognition when coated with PEG, a hydrophilic and biocompatible polymer. An example of such NPs is the PEG-*b*-poly-D,L-lactide, which contain encapsulated DOX and a superparamagnetic NPs cluster. The loading capability of DOX was only 2.7%. Improved release was realized by protonation of DOX under low pH conditions. When the pH was physiological, 1.7% of the drug was released. However, when reaching the pH value of 5, the release rate increased almost six times, up to 10.4%, in six hours. Another example is a multilayered core-shell nanocarrier. A triblock copolymer, methoxy polyethylene glycol–*block*–polymethacrylic acid–*block*–polyglycerol monomethacrylate (MPEG-*b*-PMAA-*b*-PGMA), was attached by a PGMA block to a superparamagnetic Fe_3O_4 core. The used cytostatic is adriamycin (ADR), encapsulated into the PGMA-coated core by simply blending them in an aqueous solution at physiological pH. When reaching a pH lower than 5.5, the drug was released. This formula showed low cytotoxicity because of the MPEG shell [58].

Some studies achieved the synthesis of magnetic and pH-responsive drug delivery systems by joining core Fe_3O_4 NPs, coated with SiO_2 and with a modified imidazole group, PEG-polypeptide (mPEG–poly-L-Asparagine), which provides the pH-sensitive property and increases the efficiency of the drug encapsulation. A condensation reaction was used in order to graft the block copolymer, PEG-polypeptide, to the magnetic NPs. This kind of systems forms core-shell corona structures, with the magnetic nanoparticle as core, the polymer as shell and the MPEG segment being the corona. The MPEG segment extends the lifetime in the blood flow. The drug encapsulated into the nanosized carrier was DOX. When the pH value was 7.4, less than 35% of the drug was released in 50 hours; when the pH value dropped to 5.5, 80% of the drug was released in the same amount of time [59].

To improve targeted drug delivery in cancer therapy, a system consisting of titanium oxide encapsulated iron oxide NPs (Fe_3O_4@TiO_2) have been developed. An anticancer drug, DOX, was loaded in the core-shell structure. Fe_3O_4@TiO_2 nanoparticles display pH sensitive release of DOX in the desired area. These NPs could be used in the treatment of cancer with chemo-sonodynamic therapy [60, 61].

Targeted delivery of cytostatic drugs by means of nanoparticles rise the efficiency and half-life of the drugs and also diminishes the severe side effects of traditional drug delivery systems. As a biocompatible polymeric shell, dendrimers distinguish themselves from classical

polymers because they have high molecular uniformity, limited molecular weight distribution, specific shape and size features and highly functionalized terminal surface. Polyamidoamine (PAMAM) is a polycationic dendrimer with flexible structure. PAMAM can be used in small interfering RNA (*si*RNA) delivery for the breast cancer therapy. A magnetic nanoparticle core was coated with G4 PAMAM shell loaded with *si*RNA. Results showed that *si*RNA G4PAMAM@Fe_3O_4 complex cause cancerous cell death [62].

Also, polyamidoamine (PAMAM)-coated magnetic NPs are a possible targeted drug delivery system that can encapsulate and release anticancer drugs such as DOX, with minimal side effects. The release of DOX under external pH stimuli based on the concept that microenvironment in the proximity of and in the tumor cells is acidic. The Fe_3O_4 core was encapsulated into a PEG-modified PAMAM dendrimer and DOX was electrostatically attached to the surface. It was shown that at physiological pH, DOX release was around 15%; however, at pH 5 the quantity of drug released increased up to 80% [63].

Mesoporous silica materials (M41S) have high surface area, precise pore structure and tunable pore sizes. However, the use of mesoporous silica as a carrier in targeted drug delivery is restricted. Combining the properties of magnetic NPs and mesoporous silica a core-shell complex can be achieved for targeted drug delivery in a specific site. Recently, synthesis of mesoporous silica coated Fe_3O_4 have been made (MFeCMS). The mesoporous silica shell was synthesized using a sol–gel method and then coated onto the core. The complete core-shell complex had a particle diameter of 270 nm [64].

⊡ Conclusions and future perspectives

In the biomedical field, many efforts have been made in order to achieve multifunctional nanocomposites. Among these, magnetic nanocomposites have a great potential as drug delivery carriers. Apart from their unique magnetic properties, these nanoparticles have no limitations regarding the type of pharmaceutical drug they can encapsulate or connect to. Cancer therapy is the leading area of targeted magnetic nanoparticles used as drug delivery systems [50].

The preparation of magnetic nanoparticles as drug carriers for controlled and targeted drug delivery has become very promising for use in medical treatment and nanotechnology. Iron oxide magnetic NPs (magnetite) and their properties are a valuable class of nanosized materials. Moreover, the surface chemistry of magnetite magnetic nanoparticles allows a vast area of functionalities, such as attaching therapeutic agents to their surfaces. Magnetic NPs are intensively investigated as nanocarriers for targeted drug delivery because of their exclusive physicochemical properties [65].

Nanotechnologies that rely on magnetic NPs are intensively used for therapeutic purposes. For example, magnetic hyperthermia uses magnetic nanoparticles and a magnetic field, in order to heat and kill tumoral cells. Magnetic nanoparticles have been used in medicine for several purposes, such as magnetic resonance imaging (MRI), hyperthermia or as magnetic nanocarriers for

various drug delivery systems. In comparison to traditional drugs, magnetic nanoparticles carriers with incorporate pharmaceutical drug exhibit unique characteristics, such as ability to preserve the drug from degradation while traveling to the desired site in the human body and controlled release.

Over the years, considerable progress has been made in the area of synthesis of magnetic NPs. Different sized nanoparticles can be synthesized using a vast range of procedures: coprecipitation, high temperature reactions, microemulsion techniques, sol–gel reactions, polyol processes, sonolysis and aerosol methods. Structure and pharmacokinetic relationship is also an important characteristic of superparamagnetic-based drug delivery platforms. The surface coating and also the distribution of the coating onto the iron oxide surface will not only establish the final size of the carrier, but is also an important factor in vascular clearance and biodistribution [46].

Superparamagnetic NPs based drug delivery systems provide a wide area of new possibilities for some clinical applications. In some cases, local treatment is highly advantageous because it allows a low drug dose administration, resulting in a decrease of drug-induced toxicity. Magnetic-influenced localization of pharmaceutical agents is an encouraging concept that promotes the efficiency and safety therapy administration, resulting in patient compliance. Core-shell systems with iron oxides as core and polymers as shell have been investigated as drug delivery systems for cancer therapy. Due to the improvement of surface functionalization, specificity in drug release sites can be achieved by, for example, coating with pH-responsive polymers such as PDMAEMA [66].

Core-shell NPs have unique combined properties such as lower cytotoxicity, higher dispensability, biocompatibility and chemical and thermal stability. The shell provides safety for the core while passing through the blood flow and also increases its biocompatibility. Moreover, the pH responsive property of the shell materials offers the possibility of controlled release of anticancer drugs into the exact specific tumor site by means of pH change. There have been many studies regarding core-shell structures used in cancer therapy, from which we can mention: β-thiopropionate–polyethylene glycol-modified Fe_3O_4@$mSiO_2$, PAA and FA coating of the iron oxide nanoparticle core, PDMAEMA, Fe_3O_4@SiO_2, (MPEG-*b*-PMAA-*b*-PGMA) attached by a PGMA block to a Fe_3O_4 core, Fe_3O_4 NPs core coated with SiO_2 with an imidazole group modified PEG-polypeptide (mPEG-poly-L-Asparagine), Fe_3O_4@TiO_2, PEG-modified PAMAM dendrimer shell with Fe_3O_4 core and mesoporous silica coated on Fe_3O_4, mostly coated with an anticancer drug (DOX). All these studies showed controlled release of the anticancer drug when reaching the required pH value, supporting the relevance of these NPs in cancer therapy.

Conflict of interests

The authors declare that they have no conflict of interests.

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